REMARKS

Claims 1, 2, 4, 7-12, and 14 are pending in the application. No new matter has been added.

Claims 1, 11, and 12 have been amended. Amendments to the claims should in no way be construed as an acquiescence to any of the Examiner's rejections. Such amendments are submitted solely to more particularly point out and distinctly claim the invention and to expedite the prosecution of the application. Applicant reserves the right to pursue the claims as originally filed in this or a separate application(s). Support for the amendments to claims 1, 11 and 12 can be found throughout the Specification, and specifically, for example, in paragraphs [0076] and [0158].

In light of the claim amendments and the following remarks, Applicant respectfully requests that the Examiner withdraw the rejections and pass this case to issuance.

Priority

The Examiner states that application serial nos. 60/116,748, 60/127,142 and parent application no. 09/491,896 fail to provide an enabling disclosure for the invention claimed in claims 1, 2, 4-12 and 14 for the reasons discussed under the rejection under 35 U.S.C. § 112, first paragraph. Applicant disagrees with this assessment, and submits that the priority documents indeed provide adequate support for the claimed invention. The issue here is one of enablement, not priority. If Applicant prevails on enablement, clearly there is no basis for challenging Applicant's priority claim. Accordingly, Applicant requests that the Examiner withdraw the objection to the priority claims.

Rejection of Claims 1, 2, 4, 7-12, and 14 Under 35 U.S.C. § 112, First Paragraph, Enablement

Claims 1, 2, 4, 7-12, and 14 stand rejected under 35 U.S.C. § 112, first paragraph, because the specification "does not reasonably provide enablement for a composition comprising any vector encoding any NMDA receptor antigen, nor for a method of modulating or delaying

onset of epilepsy, stroke, or decreased cognition in any subject, by administration of any vector encoding any NMDA receptor antigen." Applicant respectfully traverses this rejection.

As amended, independent claims 1, 11 and 12 are directed to *inhibiting N-methyl-D-aspartate activity* through the production of *NMDA receptor antibodies*. Applicant believes that the claims as amended are enabled and that one of ordinary skill in the art would recognize that the claimed invention is useful for the recited disorders, and s/he can "make and use" the claimed invention without any undue experimentation.

The Examiner states that the specification fails to enable "administration of any vector encoding any NMDA receptor antigen." The current specification provides ample guidance on how to make and use vectors in DNA vaccination, for example see section I: Antibodies, paragraphs [0116]-[0119] and section IV: Delivery Systems, paragraphs [0134]-[0148], their administration, *see* paragraphs [0120]-[0133], and the use of NMDA receptor antigens, *see* paragraphs [0086]-[0089]. In addition, Applicant submits a copy of the Declaration of Dr. Matthew During pursuant to 37 C.F.R §1.132 previously submitted during the prosecution of US Patent Application No. 09/491,896. The Declaration provides evidence to support the concept of administration of antigens in a vector to elicit production of antibodies capable of crossing the blood-brain barrier that modify the function of the NMDA receptor as taught by the Applicant's specification. The Declaration also supports the Applicant's position that the teachings in the specification are sufficient to allow one skilled in the art to practice the invention without undue experimentation.

The Examiner further states that "a method of modulating or delaying onset of epilepsy, stroke, or decreased cognition in any subject" is not enabled. However, as stated in MPEP 2164.02, "[a]n *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a 'working example' if that example 'correlates' with a disclosed or claimed method invention." An animal model is acceptable where it is recognized in the art that this model correlates to a specific condition. If this has not yet been established in the art, the animal model is acceptable if one skilled in the art would accept the model as *reasonably correlating* to the condition.

This "reasonableness" standard serves to distinguish the enablement requirement

of the patent laws from the more stringent standards of the FDA. Moreover, as the Examiner is aware, considerations made by the FDA for approving clinical trials are very different from those made by the PTO in determining whether a claim is enabled, *i.e.*, safety considerations are more properly left with the FDA. *Scott v. Finney*, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994).

Furthermore, Applicant has demonstrated the neuroprotective effect against epilepsy using a well established and art recognized animal model for epilepsy as seen in example 3. In these experiments, rats were vaccinated with a gene encoding an NMDAR antigen. Circulating antibodies were produced in the circulatory system of these animals soon after vaccination. The presence of these antibodies was detected in the blood at 4 weeks post vaccination, and continued to remain in the circulation for at least 4 months afterwards (*See* Figure 3B, lanes 3 and 4, respectively).

Applicant demonstrated the neuroprotective effect of these circulating antibodies by inducing epileptic seizures in these animals. In Example 3, Applicant shows that the circulating antibodies were able to cross the blood-brain barrier and bind to the target receptor on the neuronal cell, in the central nervous system of the animal *i.e.,* the NMDA receptor, and modify the function of the target receptor to protect the animal from having seizures.

Applicant also demonstrated the anti-stroke and ischemic neuroprotection efficacy of the neuroprotective vaccine using an art recognized animal model for stroke (*See* Example 4, at page 64). Applicant further demonstrated that the neuroprotective effect of the neuroprotective vaccine can occur either by directly modifying the function of the target receptor, or by modifying the function of a downstream process that involves the target receptor *i.e.,* indirect modification (*See* Example 6, at page 66 and page 70, line 8 through page 71, line 12 and Fig. 10C).

The Examiner also states that "the instant specification does not provide guidance teaching which conditions will sufficiently compromise the BBB to the extent that sufficient amounts of antibodies are able to cross and produce the desired effect." Applicants point out that "following a neuronal insult, the blood-brain barrier has increased permeability to serum antibodies, and transport and subsequent binding to the target protein can occur. This 'on

demand' or selective delivery of the neuroprotective agent (the autoantibody) limited both spatially to the site of injury and to the precise timing of injury is an advantageous feature of the invention." (See, page 64, lines 1-5). Applicants submit that the specification clearly teaches that neuronal insults can increase permeability of the blood-brain barrier as supported by the Declaration and studies performed by others as mentioned above.

The Examiner states on page 4 of the Office Action dated December 17, 2008, that "the capability of circulating antibodies to cross the blood brain barrier does not address the unpredictability inherent to the art of DNA vaccination." However methods of DNA vaccination as listed in the claims are well known in the art. Over 90 clinical trials are currently active that utilize DNA vaccination methods. Furthermore, the current specification provides ample guidance on how to make vectors and their use in DNA vaccination, for example see section I: Antibodies, paragraphs [0116]-[0119] and section IV: Delivery Systems, paragraphs [0134]-[0148]. Moreover, in terms of quantity, Applicant states that the dose and effective amount can be determined based on the characteristics of the active compound and provides a non-limiting range with doses varying according to the size, sex and weight of the subject (*See* page 30, lines 3-25).

Applicant believes that the claim amendments and remarks obviate the Examiner's rejections, and therefore request that the rejections under 35 U.S.C. §112, first paragraph, be withdrawn. Upon withdrawal of the §112, first paragraph, rejection, Applicant requests that the Examiner also withdraw the objection to the priority claims.

Rejection of Claims 1, 2, 4,7, 8, and 10 Under 35 U.S.C. §103(a)

Claims 1, 2, 4, 7, 8, and 10 have been rejected under 35 U.S.C. § 103(a), as being unpatentable over Lissin *et al.* (PNAS 95: 7097-7102 (1998)) in view of Kammescheidt et al. (1996). Applicant respectfully traverses this rejection.

Lissin describes *increasing expression* of NMDA receptors in hippocampal neurons using adenoviral expression to *increase activity* in the receptors. Nowhere in Lissin is there mention of *inhibiting NMDA activity*. In fact, Lissin's focus is to *increase NMDA activity* as a method of elucidating NMDA receptor signaling from other receptors found in neuronal synpases, effectively teaching away from a composition that would *inhibit NMDA activity*.

Conversely, the claimed invention is directed to a composition to *inhibit NMDA activity* that is capable of eliciting production NMDA receptor antibodies. There is no suggestion or teaching in the reference that would encourage one skilled in the art to use the reagent of Lissin to *inhibit NMDA activity*.

In addition, the combination with Kammescheidt, which is directed to viral transduction of hippocampal cells, does not overcome the deficiencies of Lissin since there are still no teachings or suggestions to *inhibit NMDA activity* with a composition comprising a vector to elicit production of *NMDA receptor antibodies that inhibit NMDA activity*. Accordingly, the Examiner is respectfully requested to withdraw the obviousness rejections.

CONCLUSION

In view of the above remarks, Applicants' respectfully request reconsideration and allowance of the application. The Examiner is invited to call the undersigned at (617) 439-2948 if there are any questions.

The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 141449, under Order No. 106604-7.

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Respectfully submitted,

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